Merging Basic Science and Population Science to Elucidate Mechanisms of Breast Cancer Development:

The Women's Environment, Cancer and Radiation Epidemiology (WECARE) Study

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Overview

- Context for the WECARE Study
- WECARE Study Design
- Study Organization
- Current Funding and WECARE II Planned
- “Lessons Learned”

The Epidemiology of Second Primary Breast Cancer

- Rare cancer -- 5-10% of women with breast cancer develop a second primary in the contralateral breast
- Breast cancer patients are 2-5 times more likely to develop another breast cancer than are women without breast cancer to develop a first breast cancer
- Risk of second primary breast cancer remains elevated for 30 years after first primary

Risk Factors for Second Primary Breast Cancer

Factor	RR
Early age of primary breast cancer	1.9-2.5
First Primary Lobular Histology	1.8-2.4
Family History of Breast Cancer	1.5-3.0
Mutation carriers	
BRCA1/2,	3.0-5.0
CHEK2, ATM, p53	??

Treatment and Risk of Second Primary Breast Cancer

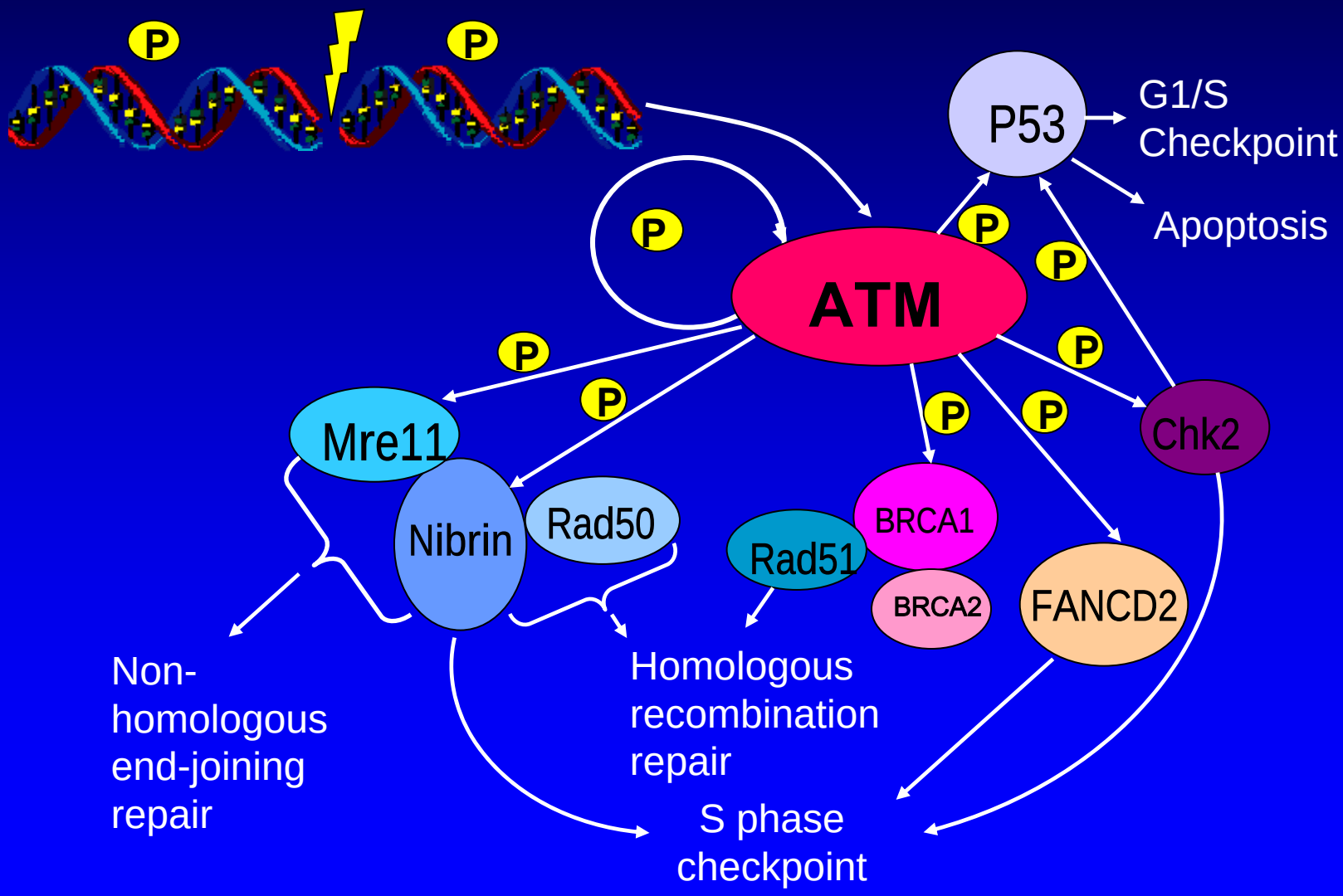
Factor	RR
Tamoxifen	<1.0
Chemotherapy	<1.0
Radiation treatment	> 1.0

Scatter dose from RT can be substantial 1.0-7.1 Gy. Excess risk range ~5.5-10.7 cases/104 woman-years/Gy.

Ataxia-Telangiectasia

- Autosomal recessive disorder
- Incidence ~1/100,000 live births
- Characterized by progressive neuronal degeneration, immunologic deficiency, radiosensitivity, premature aging/death, and increased risk of cancers
- A-T patients have mutations in both copies of the ATM gene and lack the ability to produce functioning ATM protein -- truncating mutations

Role of ATM in Cellular DNA Damage Response



ATM Heterozgosity and Breast Cancer: Few Studies, Mixed Results

Study	RR
Family Studies (Obligate +/-)	1.0-6.0
Missense Mutations	1.0-15.7
Truncating Mutations	0.5-1.0
Radiation and ATM	1.0-5.8

WECARE Study Design

Design

Population-based, case-control study

- Cases are women with bilateral breast cancer
- Controls are women with unilateral breast cancer

Hypothesis

Women who are carriers of a mutation in the ATM gene are more susceptible to radiation-induced breast cancer than are non-carriers.

(Bernstein, … , Thompson, *Br Ca Res* 2004)

WECARE Study Design

Premise

Restrict study sample to women with first primary breast cancer and study determinants of second breast cancer

- Power to detect main effects (of relatively rare genetic mutations) and interactions with environmental factors enhanced

(Begg…*JNCI* 1996)

WECARE Study Design

Considerations

To examine ATM gene-radiation interaction hypothesis:

- Rare cancer, large sample size required
- Gene large and complex, mutations rare
- Radiation exposure difficult to measure

Required Expertise: Epi, Molecular Genetics, Radiation Dosimetry/biology, and Statistical Genetics and Methodology

WECARE Study Design

Cases (n=713)

- Diagnosed since 1/1/1985 with incident breast cancer
- Diagnosed since 1/1/1986 with contralateral breast cancer
- One year or longer time lag between primaries
- Under age 55 at diagnosis of the first primary
- No other cancer diagnosis
- Alive

WECARE Study Design

Controls (n=1397)

- With unilateral breast cancer
- Individually matched 2:1 to cases on:
  - Registry
  - Age (5 year)
  - Diagnosis date of breast cancer (4 year)
  - Race
- No other cancer diagnosis
- Counter-matched on radiotherapy status
  - 2:1 (RRT+: RRT -)

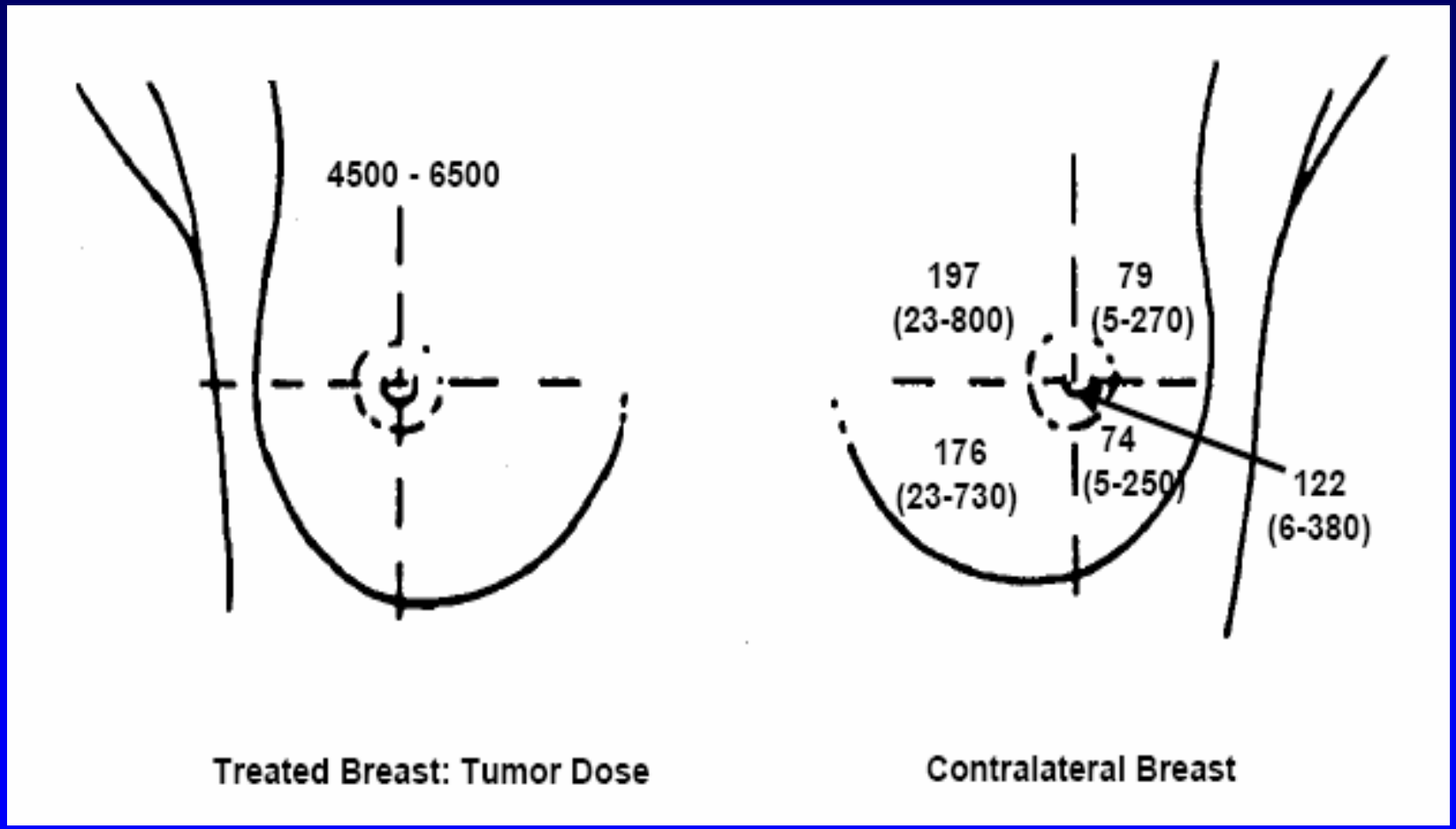
WECARE Study Data Collection

- Women identified through 5 population-based cancer registries (US and Denmark)
- Telephone interview using a structured questionnaire
- During home visits, a blood sample drawn by a study phlebotomist
  - Blood sent to: labs ATM gene analysis; biorepository at MSSM; and Coriell for cryopreservation

Medical Treatment Information and Data for Radiation Dosimetry

- Sources
  - Treatment and tumor characteristics information collected registry records
  - Hospital charts
  - Pathology/surgery reports
  - Doctor office /mammography records
  - Radiation oncology files
- Missing Data
  - ~ 7% patient records inadequate for dosimetry
  - ~ 2% participants have all documentation missing

Contralateral Breast Dose (cGy): Mean and Range among Patients Treated with Breast Irradiation (1488 patients)



ATM Gene Screening

- **ATM Gene Analyses**
  - **Conducted in 4 labs for all 2100 WECARE Study participants (US and Norway)**
  - **Staged approach: DHPLC followed by direct sequencing**
  - **All conditions, primers standardized across labs**
  - **Inter- and Intra-lab QC implemented**

(Bernstein, … , Concannon, *Hum Mut* 2003)

PRELIMINARY RESULTS

Risk of Developing Second Primary by Age at Diagnosis and Time Since First Primary

		#Cases			
Age[1]	Time[2]	RT+	RT-	RR[3]	95%CI
<45	0-4	90	85	1.1	0.8 - 1.5
<45	5+	72	64	1.4	1.0 - 2.2
45+	0-4	109	120	0.9	0.7 - 1.2
45+	5+	75	93	1.1	0.8 - 1.6

[1]Age at diagnosis of the first primary;
[2]Time since first primary breast cancer;
[3] Adjusted for exact age at first primary, age at menarche, nulliparity, family history of br ca, chemo

Distribution (%) of 713 Cases by At-Risk Period and Age

	Age at 1st primary				
Risk Period	<40	40-44	45-49	50-54	Total
0-4	11	14	16	16	57
5-9	8	7	10	9	34
10+	1	3	3	2	9
Total	20	24	29	27	100

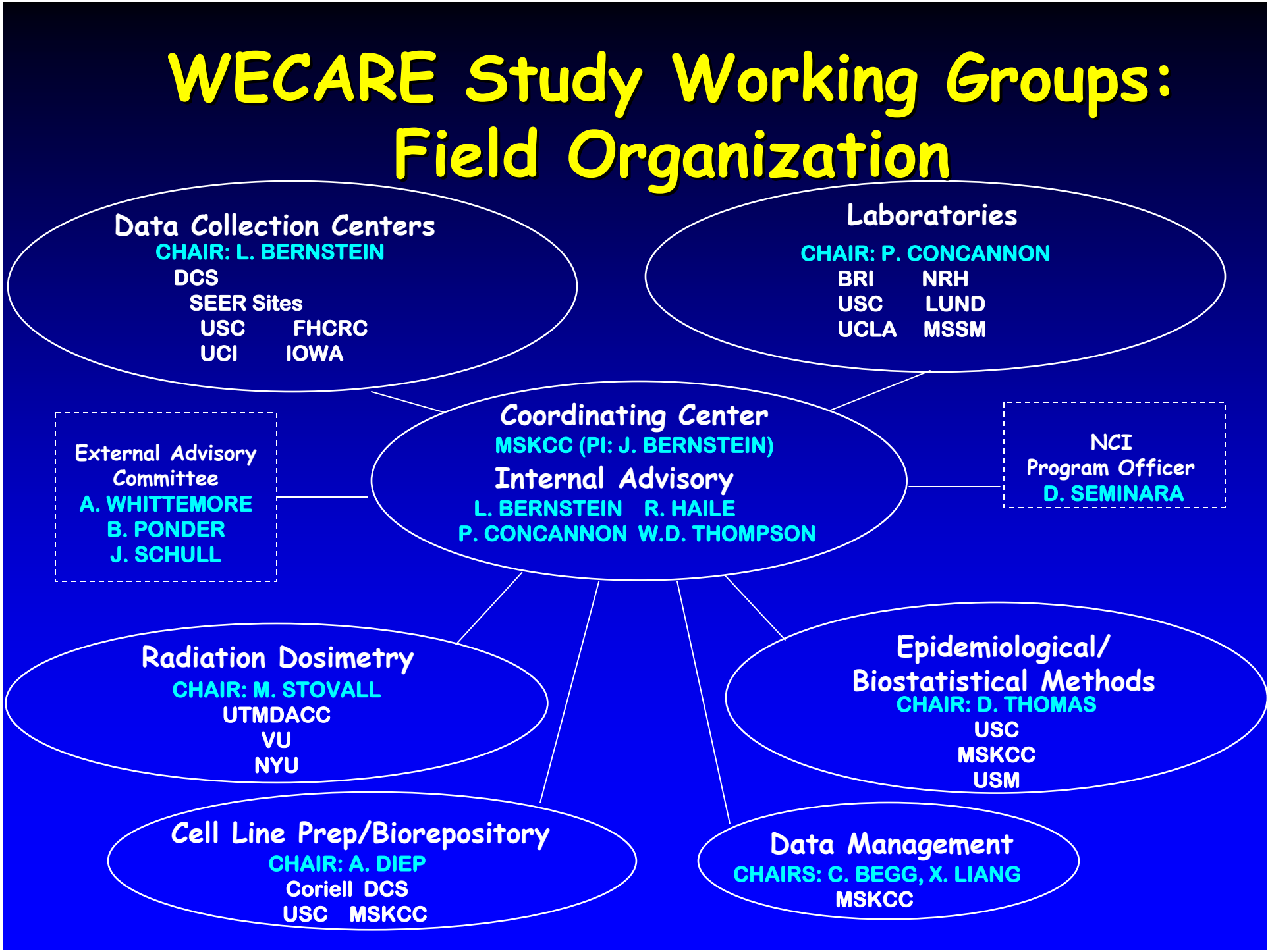
Risk of Developing Second Primary Breast Cancer by Radiation Exposure among Carriers of Deleterious ATM Mutations

ATM Carrier Status	Cases		Rate Ratio*	95% CI
	RT+	RT-		
WT	129	142	1.0	0.7 - 1.3
Possible	30	28	1.2	0.7 - 2.0
Likely	22	12	3.6	1.3 - 6.8

*Adjusted for exact age at first primary, age at menarche, nulliparity, family history of br ca, chemo

WECARE Study Organization

WECARE Study Working Groups: Field Organization



WECARE Study Working Subcommittees

WECARE Study Collaborative Group

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Other On-Going WECARE Studies

2001-2007	Interaction of Radiation, BRCA 1/2, and Breast Cancer (NCI; PI: Bernstein)
2005-2008	ATM Mutations in Breast Cancer – A Functional Approach (NCI; PI: Concannon)
2005-2009	Breast Cancer, Radiation and the ATM-Chek2 Pathway (NCI; PI: Bernstein)
2003-2005	Chek2*1100delC (DCS; PI: Olsen)

Planned WECARE Study II

Goal

To follow-up initial ATM gene-radiation interaction findings:

- Focus on long latency and youngest cases
- Increase cases → more data collection centers needed
- Maintain consortium infrastructure

Lessons Learned: Interdisciplinary Partnerships

What Worked Well

- Study Team Composition- Broad and Deep
  - Expertise in every aspect of the study
  - Prior track record and collaboration with other team members
- Working Group Communication-Constant
  - Within Group
    - Bi-monthly conference calls
    - Monthly data delivery and progress reports
    - Dedicated web-site
  - Between Group
    - Annual/ semi-annual key investigator meetings
- Internal Advisory Group- Accessible
- Support from NCI

Lessons Learned: Interdisciplinary Partnerships

What Didn't Work as Well

- Overall Communication
  - Annual meetings and e-mails barely adequate
- Committees Formed Post Hoc
  - Subcommittees
- Study Team Composition
  - Ideal mix would include junior and senior investigators
- Funding
  - Difficult to maintain infrastructure now that WECARE: ATM funding is finished